REMARKS

Claims 1, 4-34, 36, 45, 46, 86-90, 157-181, 183, 212, 213, 263-267 and 280-296 were pending in the application. In the Office Action mailed December 15, 2006, 1, 4-34, 36, 45, 86, 87, 89, 90, 157-181, 183, 263-265, 280-283, and 293-296 are rejected (claims 46, 88, 212-213 and 266-267 having been withdrawn from consideration as drawn to non-elected species).

Claims 157-181 and 183 are cancelled without prejudice, since these claims were redundant to claims 10-34 and 36, respectively.

Claims 1, 10, 36, 89, 90, 263, 264, 280, and 293-296 are amended for purposes of clarity. Claims 1, 10, 36, 89, 90 and 293-296 are amended to clarify that the expression levels are nucleic acid expression levels. This amendment is supported in the specification, for example, at page 7, lines 13-18 and 28-32; page 14, line 30 to page 16, line 28; page 64, line 33 to page 65, line 17; page 66, lines 16-26; and page 69, lines 24-25. Claims 1 and 293-296 are amended to clarify that the measuring is performed *in vitro*, as supported in the specification, for example, at page 13, lines 6-9; page 64, line 33 to page 65, line 17; page 66, lines 16-26; and page 69, lines 24-25. Claim 10 is amended to clarify that both measuring steps recited in claim 1 are performed by the recited method. Claim 10 is also amended to recite "in the genome of an organism from which said cell sample is derived," consistent with the language of claim 157 as originally filed. Claims 263, 264 and 280 are amended to delete dependency upon a cancelled claim. Claim 293 also is amended to depend additionally upon claims 5 and 6, as supported in the specification at page 13, lines 17-22.

No new matter has been added by the amendments.

Entry of the foregoing amendments and consideration of the following remarks are respectfully requested.

THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN

Claims 1, 4-34, 36, 45, 86, 87, 89, 90, 157-181, 183, 263-265, 280-283, and 293-296 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The Examiner contends that "[t]here is no direction or guidance in

the specification to show that the methods recited in claims 1, 4-34, 36, 45, 86, 87, 89, 90, 157-181, 183, 263-265, 280-283, and 293-296 can be performed," and that "there is no predictability whether [the method of claims] 1, 4-34, 36,45,86, 87, 89, 90, 157-181, 183, 263-265, 280-283, and 293-296 can be performed" (Office Action, third paragraph, page 3). The Examiner makes three contentions in support of his rejection. First, the Examiner contends that "although expression levels of different individual exons or different individual multiexons can be measured either in mRNA level or protein level, since the claims are not limited to measure exon expression in mRNA level and the specification does not provide adequate guidance to measure expression levels of different individual exons or different individual multiexons in protein level, it is unclear how to measure expression levels of different individual exons or different individual multiexons in protein level" (Office Action, first paragraph at lines 2-7, page 4). Second, the Examiner contends that "since the claims can be read as a method for analyzing exon expression in in vivo, since the claims are not be limited to a method in *in vitro* and does not indicate how to measure exon expression in in vivo, it is unclear how to measure exon expression in a cell sample in in vivo" (Office Action, first paragraph at lines 7-10, page 4). Third, the Examiner contends that "since the claims do not require that the plurality of different genes are known genes and it is known that real-time RT-PCR different individual exons or different individual multiexons requires some primers with known sequences, it is unclear how to measure expression levels of a plurality of different individual exons or different individual multiexons in each of the plurality of different unknown genes in the genome of an organism with unknown sequences" (Office Action, first paragraph at lines 13-18, page 4). Applicants respectfully disagree for the following reasons.

While disagreeing with the Examiner's first contention, Applicants have amended claim 1 in order to expedite prosecution. The amended claim 1 recites "measuring, *in vitro*, the **nucleic acid** expression levels of a plurality of different individual exons or different individual multiexons." As such, the measured expression levels are nucleic acid expression levels not protein expression levels. Therefore, the Examiner's first contention in support of unpredictability based on measuring protein levels is moot. The other rejected claims depend, directly or indirectly, on claim 1. Applicants respectfully request the Examiner to withdraw the present rejection based on the first contention.

While disagreeing with the Examiner's second contention, Applicants have amended claim 1 in order to expedite prosecution. The amended claim 1 specifies that the measuring

steps are performed ***in vitro***. Therefore, the Examiner's second contention in support of unpredictability based on measuring exon expression *in vivo* is also moot. The other rejected claims depend, directly or indirectly, on claim 1. Applicants respectfully request the Examiner to withdraw the present rejection based on the second contention.

With regard to the Examiner's third contention, Applicants respectfully submit that although the methods as claimed in the instant application require at least partial nucleic acid sequence information for probe design purposes or the use of probes with appropriate known specificity, the scope of the present invention is not overbroad. To the extent that complete sequence information may not be available for *all* genes of all genomes, this does not deny the enablement of the claimed invention because there is sufficient sequence information in the prior art for one skilled in the art to broadly practice the claimed invention for various exon/multiexons and exon variants of various genes. It is well settled patent law that an allowable claim may contain some inoperable elements:

> [M]any patented claims read on vast numbers of inoperative embodiments in the trivial sense that they can and do omit 'factors which must be presumed to be within the level of ordinary skill in the art,' *In re Skrivan*, 427 F.2d 801, 806, 57 CCPA 1201 (CCPA 1970), and therefore read on embodiments in which such factors may be included in such a manner as to make the embodiments inoperative. There is nothing wrong with this so long as it would be obvious to one of ordinary skill in the relevant art how to include those factors in such manner as to make the embodiment operative rather than inoperative.
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> *Application of Cook,* 439 F.2d 730, at 735 (C.C.P.A. 1971), and
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> Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid. 'It is not a function of the claims to specifically exclude . . . possible inoperative substances. . . .' *In re Dinh-Nguyen,* 492 F.2d 856, 858-59, 181 USPQ 46, 48 (CCPA 1974) (emphasis omitted). *Accord, In re Geerdes,* 491 F.2d 1260, 1265, 180 USPQ 789, 793 (CCPA 1974); *In re Anderson,* 471 F.2d 1237, 1242, 176 USPQ 331, 334-35 (CCPA 1973).

Atlas Powder Co. v. E.I. Du Pont de Nemours & Co., 750 F.2d 1569, at 1576, (Fed. Cir. 1984). Clearly, one skilled in the art could practice the present invention based on available sequence information or probe specificity information, and/or could obtain desired sequence information using sequencing techniques well known in the prior art. The number of any inoperative or non-enabled embodiments due to lack of genomic sequence is not significant enough to adversely affect enablement, in view of the large amount of sequence information available in the art. Indeed, according to the United States Patent and Trademark Office:

> Advances over the past ten years [have occurred] in automated sequencing and polynucleotide characterization techniques.... The entire genome of several organisms ... has been determined and deposited into nucleotide sequence databases....
>
> The GenBank® database in 1996 contained 651,972,984 nucleotides in 1,021,211 sequences. In 2000 the database contained 11,101,066,288 nucleotides in 10,106,023 sequences, about a seventeen-fold increase in the number of nucleotides and about a tenfold increase in the number of sequences.

United States Patent and Trademark Office Notice entitled "Examination of Patent Applications Containing Nucleotide Sequences," dated February 22, 2007.

Accordingly, as of the effective filing date of the instant application in 2000, there was a large amount of sequence information, as well as routine methods for nucleic acid sequencing and characterization, available to one skilled in the art. Thus, one skilled in the art would not require undue experimentation to practice the invention as claimed. Applicants respectfully request the Examiner to withdraw the present 35 U.S.C. § 112 rejection of claim 1 based on the third contention. Claims 4-34, 36, 45, 86, 87, 89, 90, 157-181, 183, 263-265, 280-283, and 293-296 ultimately depend from claim 1. Accordingly, the present 35 U.S.C. § 112 rejection of claims 4-34, 36, 45, 86, 87, 89, 90, 157-181, 183, 263-265, 280-283, and 293-296 should also be withdrawn.

CLAIMS 284-292

Applicants further respectfully point out that the Office Action summary lists claims 284-292 as rejected. However, the body of the Office Action does not contain any rejection of claims 284-292. Nevertheless, in the event that the Examiner intended to reject claims 284-292 for the reasons stated above, Applicants respectfully traverse the rejection as follows.

Claims 284 and 285 both recite "contacting a positionally-addressable array of polynucleotide probes with a sample comprising RNAs or nucleic acids derived therefrom from said cell sample...." As such, the methods as claimed in claims 284-292 are in vitro methods that measure nucleic acid expression levels. Therefore, the first and second of the Examiner's contentions do not apply to claims 284 and 285. With respect to the Examiner's third contention, the invention as claimed in claims 284 and 285 is enabled for the reasons discussed above in connection with claim 1. Accordingly, claims 284 and 285 should be allowed. Claims 286-292 ultimately depend from either claim 284 or claim 285, and thus

also should be allowed.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks into the file of the above-identified application. Applicants believe that all the pending claims are in condition for allowance. Withdrawal of the Examiner's rejections and allowance of the application are respectfully requested.

Respectfully submitted,

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